VIA ELECTRONIC FILING APRIL 9, 2010

APPELLANT'S BRIEF Address to: Mail Stop Appeal Brief Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Attorney Docket No.	10010632-3
	Confirmation No.	1968
	First Named Inventor	FISCHER, STEVEN M.
	Application Number	10/611,409
	Filing Date	June 30, 2003
	Group Art Unit	1637
	Examiner Name	TUNG, JOYCE
	Title: *METHOD OF DNA SEQUENCING USING CLEAVABLE TAGS*	

Sir:

This Brief is filed in support of the Appellant's appeal of the Final Rejection dated December 10, 2009. No claims have been allowed. Claims 21-34 and 42-44 are appealed. A Notice of Appeal was filed on February 10, 2010. As such this Appeal Brief is timely filed.

The Board of Patent Appeals and Interferences has jurisdiction over this appeal pursuant to 35 U.S.C. § 134(a).

The Commissioner is hereby authorized to charge deposit account number 50-0815, order number 10010632-3 to cover any required fee for filing the Appellant's brief. Additionally, in the event that the fee transmittal or other papers are separated from this document and/or other fees or relief are required, the Appellant petitions for such relief, including extensions of time, and authorize the Commissioner to charge any fees under 37 C.F.R. §§ 1.16, 1.17 and 1.21 which may be required by this paper, or to credit any overpayment, to the above disclosed deposit account.

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REAL PARTY IN INTEREST

The inventor named on this patent application assigned his entire rights to the invention to Agilent Technologies, Inc.

RELATED APPEALS AND INTERFERENCES

There are currently no other appeals or interferences known to the Appellant, the undersigned Appellant's representative, or the assignee to whom the inventor assigned his rights in the instant case, which would directly affect or be directly affected by, or have a bearing on the Board's decision in the instant appeal.

STATUS OF CLAIMS

Claims 21-34 and 42-44 are pending. Claims 35-41 are canceled. Claims 21-34 and 42-44 are appealed herein.

STATUS OF AMENDMENTS

None of the claims have been amended subsequent to issuance of the Final Rejection.

SUMMARY OF CLAIMED SUBJECT MATTER

The claimed invention is drawn to a method of determining a nucleic acid sequence.

Below is a description of each independent appealed claim and where support can be found in the specification.

Independent claim 21 recites a method of determining a nucleic acid sequence, said method comprising:

(a) hybridizing a primer nucleic acid to a single stranded template nucleic acid; (Specification: page 7, lines 20-22)

(b) extending said primer nucleic acid by at least one complementary nucleotide to produce an extension product that includes a 3' cleavable tag, wherein said at least one complementary nucleotide includes a 3' cleavable tag; (Specification: page 4, lines 21-23; page 7, lines 10-12)

(c) cleaving said 3' cleavable tag from said extension product to produce a cleaved tag, not bound to said at least one complementary nucleotide, and an extension product that includes said at least one complementary

nucleotide hybridized to said template nucleic acid sequence; and (Specification: page 5, lines 1-5, lines 15-23, page 6, lines 1-7; page 7, lines 12-16)

(d) detecting said cleaved tag away from said extension product to determine said nucleic acid sequence (Specification: page 6, lines 8-10).

Independent claim 42 recites a method of determining a nucleic acid sequence, said method comprising:

(a) hybridizing a primer nucleic acid to a single stranded template nucleic acid; (Specification: page 7, lines 20-22)

(b) extending said primer nucleic acid by at least one complementary nucleotide to produce a single extension product that includes a 3' cleavable tag, wherein said at least one complementary nucleotide includes a 3' cleavable tag; (Specification: page 8, lines 2-5)

(c) cleaving said 3' cleavable tag from said single extension product to produce a cleaved tag not bound to said at least one complementary nucleotide, and an extension product that includes said at least one complementary nucleotide hybridized to said template nucleic acid sequence; (Specification: page 5, lines 1-5, lines 15-23; page 8, lines 14-24)

(d) detecting said cleaved tag away from said extension product; (Specification: page 6, lines 8-10, lines 13-15)

(e) repeating steps (b) to (d) and thereby determining said nucleic acid sequence. (Specification: page 6, lines 13-15; page 7, lines 15-18)

Independent claim 43 recites method of determining a nucleic acid sequence, said method comprising:

(a) hybridizing a primer nucleic acid to a single stranded template nucleic acid in a sample; (Specification: page 7, lines 20-22)

(b) extending said primer nucleic acid by a single complementary nucleotide to produce an extension product that includes a 3' cleavable tag, wherein said extension product is produced by a polymerase in the presence of four distinguishable nucleotides, each labeled with a distinguishable 3' cleavable tag; (Specification: page 5, lines 2-12; page 7, lines 10-15; page 8, lines 2-5)

(c) cleaving said 3' cleavable tag from said extension product to produce a cleaved tag not bound to said at least one complementary nucleotide

and an extension product not separated from said single stranded template nucleic acid; and (Specification: page 5, lines 15-23; page 14, lines 7-9)

(d) detecting said cleaved tag away from said extension product. (Specification: page 6, lines 8-10, lines 13-15)

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

I. Claims 21-28, 31, 33-34, and 42-43 stand rejected under 35 U.S.C. § 102 (b) as being anticipated by Schmidt (WO 99/02728).

II. Claims 29-30 and 32 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Schmidt (*supra*) in view of Singh (USPN 6,514,700).

ARGUMENT

I. Claims 21-28, 31, 33-34, and 42-43 stand rejected under 35 U.S.C. § 102 (b) as being anticipated by Schmidt (*supra*).

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil of California*, 814 F.2d 628, 631, (Fed. Cir. 1987).

Furthermore, Federal Circuit, in *Net MoneyIN, Inc. v. VeriSign, Inc.*, held that "Because the hallmark of anticipation is prior invention, the prior art reference--in order to anticipate under 35 U.S.C. § 102--must not only disclose all elements of the claim within the four corners of the document, but must also disclose those elements "arranged as in the claim.'" *Net MoneyIN, Inc.*, 545 F.3d 1359,1369 (citing *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983).

Moreover, MPEP § 2112 states that "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." Citing *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original).

The claims are directed to a sequencing method in which the template nucleic acid being sequenced and the primer extension product remain *hybridized* when a cleavable tag is cleaved from the extension product.

Specifically, claim 21 requires, *inter alia*, that cleaving the 3'cleavable tag from the extension product produces a cleaved tag and an extension product *hybridized* to the template nucleic acid. Claim 42 requires, *inter alia*, that a single extension product

(that includes a 3' cleavable tag) is produced and that cleaving the 3'cleavable tag from the extension product produces a cleaved tag and an extension product *hybridized* to the template nucleic acid. Claim 43 requires that the primer nucleic acid is extended by a single complementary nucleotide using a polymerase to produce an extension product (that includes a 3' cleavable tag) and that cleaving the 3'cleavable tag produces a cleaved tag and an extension product not separated from the template nucleic acid.

In summary and as will be described in greater detail below, the Appellants submit that Schmidt does not disclose a method in which the extension product and the template nucleic acid are hybridized and are not separated when the tag is cleaved, as required by the rejected claims. Rather, Schmidt's method is one in which a population of tagged extension products of varying lengths (Sanger ladder) are generated by extending a primer hybridized to a template nucleic acid being sequenced. The extension products and the template nucleic acid are denatured and the extension products are separated on the basis of length prior to cleavage of the tag associated with each of the individual extension product. As a result, the cleavage step in Schmidt does not produce a cleaved tag and an extension product that is hybridized to (and not separated from) the template nucleic acid. Since Schmidt's method is different to that being claimed, Schmidt cannot anticipate the claims and this rejection should be reversed.

To the extent that any further discussion is necessary, the Board is respectfully directed to the arguments below.

The following section contains arguments directed to four different groups of claims.

Arguments directed to Claims 21-34 and 42-44

The following arguments are directed to Claims 21-34 and 42-44. Claim 21 is representative of this group and is set forth below:

21. A method of determining a nucleic acid sequence, said method comprising:

(a) hybridizing a primer nucleic acid to a single stranded template nucleic acid;

(b) extending said primer nucleic acid by at least one complementary nucleotide to produce an extension product that includes a 3' cleavable tag, wherein said at least one complementary nucleotide includes a 3' cleavable tag;

(c) cleaving said 3' cleavable tag from said extension product to produce a cleaved tag, not bound to said at least one complementary nucleotide, and an extension

product that includes said at least one complementary nucleotide hybridized to said template nucleic acid sequence; and

(d) detecting said cleaved tag away from said extension product to determine said nucleic acid sequence.

Accordingly, claim 21 requires that the cleaving step (c) produce a cleaved tag and an extension product that is *hybridized* to the template nucleic acid.

Schmidt teaches a sequencing method in which a population of tagged extension products (Sanger ladder) is produced, the individual extension products are separated on the basis of their length, and after separation, the tags are cleaved and detected. See page 2, last paragraph and page 3. Specifically, Schmidt discloses that the extension products are separated one from another via capillary electrophoresis. See page 45, first full paragraph:

> are shown in Figure 15. Prior to cleavage of labels one needs to separate the Sanger ladder into its component fragment lengths. In a mass spectrometry system this stage can be coupled to the sample loading in a LCMS system. Separation into bands can be achieved by capillary zone electrophoresis. This will then pass through a UV spectrometer to determine the quantity of DNA in each band. Following this the sample will then pass through a photocleavage module to release the mass-labels which will then be injected into an electrospray mass spectrometer for analysis of the labels in each band.

(Underlining added)

Although the details of the capillary electrophoresis method by which Schmidt separates the Sanger ladder are not described in the sections cited by the Examiner, these methods are understood to require denaturation of the template nucleic acid and the primer extension products and separation of the extension products under denaturing conditions, as is described in any standard laboratory textbook such as Sambrook et al. (Molecular Cloning: A Laboratory Manual, Third Edition, (2001) Cold Spring Harbor, N.Y) and Ausubel et al., (Short Protocols in Molecular Biology, 3rd ed., Wiley & Sons, 1995). The principle of the Sanger sequencing method is well known and described in Sanger (J. Mol. Biol. 1975 94: 441–8)

Accordingly, because Schmidt discloses that the extension product is to be separated from the nucleic acid template prior to cleaving the cleavable tag from the

nucleic acid, the method of Schmidt does not include the production of a cleaved tag and an extension product which includes the at least one complementary nucleotide that is *hybridized* to the template nucleic acid sequence, as required by the appealed claims.

In attempting to establish this rejection, the Examiner argues that Schmidt discloses a method in which "a series of DNA fragments is provided by contacting a template in the presence of DNA polymerase with a mixture of nucleotides sufficient for hybridizing to the template for forming a second strand of DNA complementary to the template. The mixture comprises a set of four probes containing all four nucleotides for hybridizing to the template in which the nucleotides of each probe comprise a modified nucleotide, which is capable of polymerizing to the second strand of DNA, but blocked to prevent further polymerization and which is cleavably attached to the mass label." The Examiner further states that "Schmidt et al. also disclose an alternative implementation to use photolysable mass labels at the 3'-OH of each 4-mer oligonucleotide. The mass-label could be attached to another part of the molecule from which it can be released independently of the uncapping reaction of the 3' terminus (see pg. 46, paragraphs 4 and 5). This inherently teaches that 3' tag is cleaved from an extension product and not bound to said at least one complementary nucleotide and an extension product that includes said at least one complementary nucleotide hybridized to said template nucleic acid sequence" (see Final Office Action dated December 10, 2009, pages 2-3).

As noted above, the Examiner bases this rejection on paragraphs 4 and 5 of page 46 of Schmidt. However, paragraphs 4 and 5, page 46 of Schmidt when read in context do not disclose any method in which complementary nucleic acid and template nucleic acid remain hybridized when the 3' tag is cleaved. Rather, paragraphs 4 and 5 provide alternative methods for probing immobilized Sanger ladder which is a mixture of multiple nucleic acids of varying lengths. In the methods of both paragraphs 4 and 5, the complementary nucleic acids (i.e. the Sanger ladder nucleic acids) and template nucleic acid are separated when the 3' tag is cleaved. Thus, the cleavage step of Schmidt cannot yield a tag and an extension product that is hybridized to the template nucleic acid. The Appellant's position is supported by page 46, paragraph 1 of Schmidt which provides the context for paragraphs 4 and 5 on page 46. Paragraph 1 on page 46 of Schmidt is reproduced below:

> In one embodiment one can probe the immobilised Sanger ladder with every one of the possible 256 single-stranded 4 base oligonucleotides. Each of these would carry a unique identifying label corresponding to its known, sequence of 4 bp. In the 5' to 3' format, the label could be attached to the 3' -OH effectively blocking them from further extension, or a separate blocking group can be used and the label can be attached elsewhere in the molecule.

Paragraph 4 on page 46 of Schmidt describes that the probes are labeled and blocked at the 3'-OH end by a mass label. Thus, paragraph 4 further describes a first embodiment of the 5' to 3' format above (see lines 4-6 of paragraph 1 above). Paragraph 5 on page 46 of Schmidt describes that the probes are labeled by a mass label and blocked with a phosphate group, separating the steps of cleavage of the mass label and unblocking of the 3'-OH group. Thus, paragraph 5 further describes a second embodiment of the 5' to 3' format above (see lines 6-7 of paragraph 1 above).

Thus, Schmidt discusses that the methods described in the paragraphs 4 and 5, page 46 (cited by the Examiner) are two alternative embodiments of the *method of probing the immobilized Sanger ladder*, which method requires separating the individual component fragments of the Sanger ladder. Since Schmidt discloses that the individual component fragments of the Sanger ladder are separated from each other and the template nucleic acid and the cleavage is performed on the separated individual component fragments of the Sanger ladder, the cleavage step of Schmidt cannot produce a cleaved tag and an extension product which includes the at least one complementary nucleotide that is *hybridized* to the template nucleic acid sequence.

Furthermore, it is described throughout the disclosure of Schmidt that the cleavage step is performed on the separated component fragments of the Sanger ladder (see, for example, page 45, last paragraph; page 16, third paragraph, Fig. 4a). Thus, the cleavage step cannot produce a cleaved tag and an extension product which includes the at least one complementary nucleotide that is *hybridized* to the template nucleic acid sequence, as required by the rejected claims.

With regard to the section of paragraph 5, page 46 of Schmidt (cited by the Examiner), the Appellant submits that cited section merely discloses alternatives to the 3'-OH photolysable mass labels, such as, using dideoxynucleotides to block the 3'-OH of probe molecules and attaching the mass label to another part of the molecule so that the mass label can be released independently of the uncapping reaction of the 3' terminus. Since this step is performed on the component fragments of the Sanger ladder that have

been separated from each other and the template nucleic acid (see above), contrary to the Examiner's assertion, the cited section does not disclose that the cleavage of the tag produces a cleaved tag and an extension product hybridized to the template nucleic acid sequence.

Furthermore, it would appear that the Examiner is basing this rejection on a theory of inherency. The Appellants respectfully submit that the Examiner has not provided any rational or evidence supporting inherency to establish that Schmidt discloses a method in which the cleaving step produces a cleaved tag and an extension product hybridized to the template nucleic acid sequence. Rather, as established above, Schmidt discloses cleaving a mass label from the individual component fragments of the Sanger ladder that have been separated from each other and the template nucleic acid.

Therefore, Schmidt cannot anticipate the claimed subject matter because it fails to disclose every element of the appealed claims.

Arguments directed to Claim 42

The following arguments are directed to Claim 42.

42. A method of determining a nucleic acid sequence, said method comprising:

(a) hybridizing a primer nucleic acid to a single stranded template nucleic acid;

(b) extending said primer nucleic acid by at least one complementary nucleotide to produce a single extension product that includes a 3' cleavable tag, wherein said at least one complementary nucleotide includes a 3' cleavable tag;

(c) cleaving said 3' cleavable tag from said single extension product to produce a cleaved tag not bound to said at least one complementary nucleotide, and an extension product that includes said at least one complementary nucleotide hybridized to said template nucleic acid sequence;

(d) detecting said cleaved tag away from said extension product;

(e) repeating steps (b) to (d) and thereby determining said nucleic acid sequence.

Accordingly, step (e) of claim 42 requires, *inter alia*, repeating the steps of extending (see step b), cleaving (see step c), and detecting (see step d) and thereby determining the nucleic acid sequence.

The Appellant submits that Schmidt does not disclose the method recited in claim 42. The Examiner has not indicated where step (e) is disclosed in Schmidt. Furthermore, since Schmidt teaches a sequencing method that uses the Sanger's sequencing

method, Schmidt cannot even inherently teach the method of claim 42. As is well known, in Sanger's sequencing method, the template nucleic acid is hybridized to a primer and a series of DNA fragments of all possible lengths (Sanger ladder; see Schmidt page 2, last paragraph and page 3, for example) are generated by extension of the primer. The sequence of the template nucleic acid is deduced from the DNA fragments of the Sanger ladder. Accordingly, there is no repetition of extending, cleaving and detecting steps in Schmidt. Thus, Schmidt does not disclose a sequencing method with the step (e) recited in claim 42.

Arguments directed to Claim 43

The following arguments are directed to Claim 43.

43. A method of determining a nucleic acid sequence, said method comprising:

(a) hybridizing a primer nucleic acid to a single stranded template nucleic acid in a sample;

(b) extending said primer nucleic acid by a single complementary nucleotide to produce an extension product that includes a 3' cleavable tag, wherein said extension product is produced by a polymerase in the presence of four distinguishable nucleotides, each labeled with a distinguishable 3' cleavable tag;

(c) cleaving said 3' cleavable tag from said extension product to produce a cleaved tag not bound to said at least one complementary nucleotide and an extension product not separated from said single stranded template nucleic acid; and

(d) detecting said cleaved tag away from said extension product.

Claim 43 requires extending the primer nucleic acid by a single complementary nucleotide to produce an extension product that includes a 3' cleavable tag, wherein said extension product is produced by a polymerase in the presence of four distinguishable nucleotides (step (b) of claim 43), cleaving the 3' cleavable tag from the extension product to produce a cleaved tag not bound to the at least one complementary nucleotide and an extension product not separated from the single stranded template nucleic acid (step (c) of claim 43).

In formulating this rejection, the Examiner asserts that "Schmidt et al. also disclose an alternative implementation to use photolysable mass labels at the 3'-OH of each 4-mer oligonucleotide. The mass-label could be attached to another part of the molecule from which it can be released independently of the uncapping reaction of the 3' terminus (see pg. 46, paragraphs 4 and 5). This inherently teaches that 3' tag is cleaved

from an extension product and not bound to said at least one complementary nucleotide and an extension product that includes said at least one complementary nucleotide hybridized to said template nucleic acid sequence" (see Final Office Action dated December 10, 2009, pages 2-3).

However, paragraphs 4 and 5 disclose alternative methods for probing immobilized Sanger ladder by ligating oligonucleotides to the fragments of the Sanger ladder. In this context, Schmidt does not disclose extending the primer nucleic acid by a *single* complementary nucleotide using a polymerase to produce an extension product that includes a 3' cleavable tag and cleaving the 3' cleavable tag from the extension product to produce a cleaved tag and an extension product not separated from the single stranded template nucleic acid, as required by claim 43. Rather, a primer nucleic acid is extended by a *4-mer oligonucleotide* with a cleavable mass label and the mass label of the 4-mer oligonucleotide is cleaved. This 4-mer is added by using a *ligase*. Moreover, as established above, the cleavage step does not produce a cleaved tag and an extension product not separated from the single stranded template nucleic acid.

Even if it is assumed for the sake of argument that paragraphs 4 and 5 on page 46 teach that the extended product and the template nucleic acid are not separated before the cleavage step, Schmidt still fails to disclose extending the primer nucleic acid by a *single* complementary nucleotide using a *polymerase* at paragraphs 4 and 5 on page 46. The Appellant submits that the mere disclosure of individual elements of a claim within the four corners of a reference is not enough. Rather, to serve as an anticipatory reference, the reference should disclose all of the elements arranged or combined in the same way as recited in the claim[1].

Since Schmidt fails to disclose all of the elements of claim 43 "arranged as in the claim" (*Net MoneyIN, Inc.*, 545 F.3d at 1369 (*supra*)), Schmidt cannot anticipate claim 43 under §102.

Arguments directed to Claim 44

The following arguments are directed to Claim 44.

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[1] Finally, the Federal Circuit concluded that "We thus hold that unless a reference discloses within the four corners of the document not only all of the limitations claimed but also all of the limitations arranged or combined in the same way as recited in the claim, it cannot be said to prove prior invention of the thing claimed and, thus, cannot anticipate under 35 U.S.C. § 102 (*Net MoneyIN, Inc.*, 545 F.3d 1359 at 1371).

44. The method of claim 43, comprising repeating steps (b) to (d) on said extension product produced in step (c).

Claim 43 requires repeating the extending (see claim 43, step b), cleaving (see claim 43, step c), and detecting (see claim 43, step d) on the extension product produced from step (c) of cleaving the 3' cleavable tag from the extension product to produce a cleaved tag not bound to the at least one complementary nucleotide and an extension product not separated from the single stranded template nucleic acid.

The Appellant submits that Schmidt does not disclose the method of claim 44. The Examiner has not indicated where such a method is disclosed in Schmidt.

Since Schmidt does not disclose each and every element of claim 44, Schmidt fails to anticipate claim 44 under §102.

II. Claims 29-30 and 32 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Schmidt (*supra*) in view of Singh (USPN 6,514,700).

In order to meet its burden in establishing a rejection under 35 U.S.C. §103, the Office must first demonstrate that a prior art reference, or references when combined, teach or suggest all claim elements. *See, e.g., KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1740 (2007); *Pharmastem Therapeutics v. Viacell et al.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007); MPEP § 2143(A)(1). In addition to demonstrating that all the elements were known in the prior art, the Office must also articulate a reason for combining the elements. *See, e.g., KSR* at 1741; *Omegaflex, Inc. v. Parker-Hannifin Corp.*, 243 Fed. Appx. 592, 595-596 (Fed. Cir. 2007) (citing *KSR*). Further, the Supreme Court in *KSR* also stated that that "a court *must* ask whether the improvement is more than the predictable use of prior art elements according to their established functions." *KSR* at 1740; emphasis added. As such, in addition to showing that all elements of a claim were known in the prior art and that one of skill had a reason to combine them, the Office must also provide evidence that the combination would be a predicted success.

The Examiner states that Schmidt is deficient in that Schmidt does not disclose that the cleavable tag is a fluorescent tag and it is acid or base cleavable. Singh is cited to meet Schmidt's deficiencies.

The Appellant submits that Schmidt is also deficient in that it fails to teach or suggest all the elements of the Appellant's claims because, as noted above, Schmidt does not disclose, for example, cleaving said 3' cleavable tag from said extension product to produce a cleaved tag and an extension product that includes the at least one

complementary nucleotide hybridized to or not separated from the template nucleic acid sequence, as required by the rejected claims.

Singh was cited solely for its alleged disclosure of a fluorescent tag and tags that are acid or base cleavable. Consequently, Singh fails to remedy the deficiencies of Schmidt. Therefore, the cited combination of Schmidt and Singh does not disclose or suggest all the elements of claims 29-30 and 32, and the Appellant respectfully requests reversal of this rejection.

In view of the foregoing discussion, the Appellant respectfully requests that the rejection of Claims 21-34 and 42-44 be reversed and that the application be remanded to the Examiner with instructions to issue a Notice of Allowance.

Respectfully submitted,

Date: April 9, 2010

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CLAIMS APPENDIX

21. A method of determining a nucleic acid sequence, said method comprising:

(a) hybridizing a primer nucleic acid to a single stranded template nucleic acid;

(b) extending said primer nucleic acid by at least one complementary nucleotide to produce an extension product that includes a 3' cleavable tag, wherein said at least one complementary nucleotide includes a 3' cleavable tag;

(c) cleaving said 3' cleavable tag from said extension product to produce a cleaved tag, not bound to said at least one complementary nucleotide, and an extension product that includes said at least one complementary nucleotide hybridized to said template nucleic acid sequence; and

(d) detecting said cleaved tag away from said extension product to determine said nucleic acid sequence.

22. The method according to Claim 21, wherein said primer nucleic acid is extended by a single deoxynucleotide triphosphate labeled with a cleavable tag (cdNTP) to produce said extension product.

23. The method according to Claim 22, wherein said extension product is produced by a polymerase in the presence of four distinguishable cdNTPs.

24. The method according to Claim 23, wherein said four distinguishable cdNTPs each include a distinguishable cleavable tag.

25. The method according to Claim 21, wherein said primer nucleic acid is extended by an oligonucleotide of at least two nucleotides in length that includes a cleavable tag.

26. The method according to Claim 25, wherein said cleavable tag is a 3' cleavable tag.

27. The method according to Claim 25, wherein said extension product is produced by a ligase in the presence of said oligonucleotide.

28. The method according to Claim 21, wherein said cleavable tag is cleavable by chemical cleavage.

29. The method according to Claim 28, wherein said cleavable tag is an acid cleavable tag.

30. The method according to Claim 28, wherein said cleavable tag is a base cleavable tag.

31. The method according to Claim 21, wherein said cleavable tag is a photocleavable tag.

32. The method according to Claim 21, wherein said cleavable tag is a fluorescent tag.

33. The method according to Claim 21, wherein said cleavable tag is a mass tag.

34. The method according to Claim 21, wherein said steps (a) to (d) are repeated at least once.

42. A method of determining a nucleic acid sequence, said method comprising:

(a) hybridizing a primer nucleic acid to a single stranded template nucleic acid;

(b) extending said primer nucleic acid by at least one complementary nucleotide to produce a single extension product that includes a 3' cleavable tag, wherein said at least one complementary nucleotide includes a 3' cleavable tag;

(c) cleaving said 3' cleavable tag from said single extension product to produce a cleaved tag not bound to said at least one complementary

nucleotide, and an extension product that includes said at least one complementary nucleotide hybridized to said template nucleic acid sequence;

(d) detecting said cleaved tag away from said extension product;

(e) repeating steps (b) to (d) and thereby determining said nucleic acid sequence.

43. A method of determining a nucleic acid sequence, said method comprising:

(a) hybridizing a primer nucleic acid to a single stranded template nucleic acid in a sample;

(b) extending said primer nucleic acid by a single complementary nucleotide to produce an extension product that includes a 3' cleavable tag, wherein said extension product is produced by a polymerase in the presence of four distinguishable nucleotides, each labeled with a distinguishable 3' cleavable tag;

(c) cleaving said 3' cleavable tag from said extension product to produce a cleaved tag not bound to said at least one complementary nucleotide and an extension product not separated from said single stranded template nucleic acid; and

(d) detecting said cleaved tag away from said extension product.

44. The method of claim 43, comprising repeating steps (b) to (d) on said extension product produced in step (c).

EVIDENCE APPENDIX

No evidence submitted under 37 CFR §§ 1.130, 1.131 or 1.132 has been relied upon by Appellant in this Appeal.

RELATED PROCEEDINGS APPENDIX

As stated in the Related Appeals and Interferences section above, there are no decisions rendered by a court or the Board which would directly affect or be directly affected by, or have a bearing on the Board's decision in the instant appeal.